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(54) Title: A PROCESS FOR MAKING EPOXIDE INTERMEDIATES

(57) Abstract

It has been surprisingly discovered that the disadvantages of the lengthy literature procedures to synthesize 13,14-dihydro prostaglandin A, E, and F derivatives can be overcome using a novel Methyl 7-(2-hydroxy-5-(2-(2-oxiranyl)ethyl)-4-(1,1,2,2tetramethyl-1-silapropoxy)cyclopentyl) heptanoate intermediate, which can be synthesized from commercially available Methyl 7-[3-(R)-hydroxy-5-oxo-1-cyclopent-1-yl] heptanoate. This novel intermediate can be coupled with oxygen, carbon, sulfur, and nitrogen nucleophiles, in the presence of a base or a Lewis acid, in a ring-opening process to provide 13,14-dihydro prostaglandin A, E, and F derivatives.

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A PROCESS FOR MAKING EPOXIDE INTERMEDIATES

CROSS REFERENCE

This application claims priority under Title 35, United States Code 119(e) from Provisional Application Serial No. 60/058,254, filed September 9, 1997.

TECHNICAL FIELD

The present invention describes a process for making a novel epoxide intermediate useful for making 13,14-dihydro prostaglandin A, E and F derivatives.

BACKGROUND OF THE INVENTION

The present invention describes a novel process for making a novel epoxide intermediate useful for making 13,14-dihydro prostaglandin A, E and F derivatives. Naturally occurring prostaglandins (PGA, PGB, PGD, PGE, PGF, and PGI) are C-20 unsaturated fatty acids. Prostaglandin A, E, and F derivatives are distinguishable as such by the substituents on the alicyclic ring. PGA derivatives are characterized by a ketone at C_9 and a double bond between C_{10} and C_{11}. PGE derivatives are characterized by a ketone at C_9 and a hydroxyl at C_{11}. PGF derivatives are characterized by hydroxyl groups at both C_9 and at C_{11}.

Such derivatives are useful for the treatment of many medical disorders including, for example, ocular disorders, hypertension, fertility control, and osteoporosis. For example, the prostaglandin 13,14-dihydro PGF$_{1\alpha}$, disclosed in U.S. Patent No. 3,776,938 (1973) by Bergstrom, S., and Sjovall,J. of the Kemiska Institutionen, Karolinska Institute, Stockholm 60, Sweden has a stimulatory effect on smooth muscle contraction as shown by test strips of guinea pig ileum, rabbit duodenum, or gerbil colon. Further information regarding the biological effects of 13,14-dihydro PGA, PGE and PGF derivatives are disclosed in the following references: U.S. Patent No. 3,882,241 issued to Pharriss, G., May 6, 1975; G.B. Patent No. 1,456,512 (1976) issued to Pfizer Inc., Bundy, G.L.; Lincoln, F.H., "Synthesis of 17-Phenyl-18,19,20-trinor prostaglandins I. The PG1 Series", Prostaglandins Vol. 9 (1975) pp. 1-4.; CRC Handbook of Eicosanoids: Prostaglandins and Related Lipids Vol. 1, Chemical and Biochemical Aspects, Parts A & B, A.L. Willis, eds., CRC Press (1987); Liljebris, C.; et. al." Derivatives of 17-Phenyl-18,19,20-trinorprostaglandin F2α Isopropyl Ester: Potential Antiglaucoma Agents", Journal of Medicinal Chemistry Vol. 38, (1995), pp. 289-304; Collins, P.W.; Djuric, S.W. "Synthesis of Therapeutically Useful Prostaglandin and Prostacyclin Analogs", Chemical Reviews 93 (1993), pp. 1533-1564.

In the art, 13,14 dihydro prostaglandin E derivatives have been synthesized according to several different methods. Such methods include those described in the following references: Corey et al., *J. Amer. Chem. Soc.* 1969, *91*, p. 5675; Corey et al., *J. Amer. Chem. Soc.* 1970, *92*, p. 397; Corey et al., *J. Amer. Chem. Soc.* 1970, *92*, p. 2586; Corey, E.J. *Ann. N.Y. Acad. Sci.* 1971, *180*, p. 24; Corey et al., *The Logic of Chemical Synthesis*, John Wiley & Sons: New York, 1989, p. 250-266.

To date, prostaglandin E derivatives have generally been assembled through the common Corey aldehyde intermediate via introduction of the omega side-chain through Wadsworth-Horner-Emmons phosphonate chemistry, reduction and protection of the C_{15} position, introduction of the top chain via Wittig chemistry, oxidation of the C_9 position with Jones reagent, and finally, removal of the various protecting groups with the appropriate reagent(s).

Prostaglandins of the A series have generally been assembled from the PGE series by acid or base induced elimination of the C11 hydroxyl group. Methods for conversion of PGE derivatives to PGA derivatives include those described in the following references: Stork et al., *J. Amer. Chem. Soc.* 1976, *98*, p. 1583; Stork et al., *J. Amer. Chem. Soc.* 1978, *100*, p. 8272.

In the art, 13,14 dihydro prostaglandin F derivatives have been synthesized according to several different methods. Such methods include those described in the following references: G.B Patent No. 1,040,544 issued to A.C. Chapman; G.B. Patent No. 1,186,505 issued to the Upjohn Co.; U.S. Patent No. 3,505,386 issued to Babcock, J.C., and Beal, P.F.,III, April 7, 1970, U.S. Patent No. 3,435,053 issued to Beal, Lincoln, Jr., Portage, and Pike, March 25, 1969; G.B. Patent No. 1,251,750 issued to the Upjohn Co.; Bundy, G.L.; Lincoln, F.H. " Synthesis of 17-Phenyl-18,19,20-trinorprostaglandins I. The PG_1 Series" Prostaglandins, Vol. 9 (1975), pp. 1-4.

To date, the synthesis of 13,14-dihydro prostaglandin F derivatives has involved either conversion of the 13,14-dihydro prostaglandin E_1 skeleton (see Sjovall, et. al., U.S. Patent No. 3,776,938) via reduction of the carbonyl moiety at C_9 (prostaglandin numbering) to the alcohol or by exhaustive hydrogenation of the preassembled $PGF_{2\alpha}$ skeleton (see for example: Bundy, G.L.; Lincoln, F.H. "Synthesis of 17-Phenyl-18,19,20-trinor prostaglandins I. The PG_1 Series" Prostaglandins, Vol. 9 (1975), pp. 1-4.) The prostaglandin $F_{2\alpha}$ skeleton is prepared in a variety of ways; generally from the condensation of the Corey aldehyde (see for example: Corey, E.J.; Weinshenker, N.M.; Schaaf, T.K.; Huber, W. "Stereo-Controlled Synthesis of Prostaglandins $F_{2\alpha}$ and E_2 (*dl*)" J. Am. Chem. Soc. 1969, 91(20), p.5675-5677] with the appropriate oxophosphonate, followed by reduction at C_{15} (prostaglandin numbering)[see, for

example: Noyori, R,; Tomino, I.; Yamada, M.; Nishizawa, M. "Synthetic Applications of the Enantioselective Reduction by Binaphthol-Modified Lithium Aluminum Hydride Reagents" J. Amer. Chem. Soc. 1984, 106, p. 6717-6725), reduction to the lactol and addition of the C_1-C_7 (prostaglandin numbering) side-chain (see, for example: G.B. Patent No. 1,456,512, complete specification published Nov. 24, 1976). For other methods to prepare the prostaglandin $F_{2\alpha}$ skeleton for conversion into the 13,14-dihydro prostaglandin $F1\alpha$ derivatives, see: Collins, P.W.; Djuric, S.W. "Synthesis of Therapeutically Useful Prostaglandin and Prostacyclin Analogs", Chemical Reviews, 93, (1993), pp. 1533-1564.

Synthesis of 13,14-dihydro prostaglandin A, E, and F derivatives using the methods described above is somewhat lengthy and expensive. Thus, it would be desirable to have a method that is higher yielding, more economical, and that involves fewer steps for preparing 13,14-dihydro prostaglandin A, E, and F derivatives.

SUMMARY OF THE INVENTION

It has been surprisingly discovered that the disadvantages of the lengthy literature procedures to synthesize 13,14-dihydro prostaglandin A, E, and F derivatives can be overcome using a novel Methyl 7-(2-hydroxy-5-(2-(2-oxiranyl)ethyl)-4-(1,1,2,2 tetramethyl-1-silapropoxy)cyclopentyl) heptanoate intermediate, which can be synthesized from commercially available Methyl 7-[3-(R)-hydroxy-5-oxo-1-cyclopent-1-yl] heptanoate. This novel intermediate can be coupled with oxygen, carbon, sulfur, and nitrogen nucleophiles, in the presence of a base or a Lewis acid, in a ring-opening process to provide 13,14-dihydro prostaglandin A, E, and F derivatives.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a process for making a novel Methyl 7-(2-hydroxy-5-(2-(2-oxiranyl)ethyl)-4-(1,1,2,2 tetramethyl-1-silapropoxy)cyclopentyl) heptanoate intermediate (the "epoxide intermediate"). This epoxide intermediate is useful for making 13,14-dihydro prostaglandin A, E and F derivatives. Thus, the invention is further directed to a process for making 13,14-dihydroprostaglandin A, E and F derivatives.

Definitions and Usage of Terms

"Alkyl" is a saturated or unsaturated hydrocarbon chain having 1 to 18 carbon atoms, preferably 1 to 12, more preferably 1 to 6, more preferably still 1 to 4 carbon atoms. Alkyl chains may be straight or branched. Preferred branched alkyl have one or

two branches, preferably one branch. Preferred alkyl are saturated. Unsaturated alkyl have one or more double bonds and/or one or more triple bonds. Preferred unsaturated alkyl have one or two double bonds or one triple bond, more preferably one double bond. Alkyl chains may be unsubstituted or substituted with from 1 to about 4 substituents. Preferred alkyl are unsubstituted. Preferred substituted alkyl are mono-, di-, or trisubstituted. Preferred alkyl substituents include halo, hydroxy, aryl (e.g., phenyl, tolyl, alkyloxphenyl, alkyloxycarbonylphenyl, halophenyl), heterocyclyl, and heteroaryl.

"Aromatic ring" is an aromatic hydrocarbon ring system. Aromatic rings are monocyclic or fused bicyclic ring systems. Monocyclic aromatic rings contain from about 5 to about 10 carbon atoms, preferably from 5 to 7 carbon atoms, and most preferably from 5 to 6 carbon atoms in the ring. Bicyclic aromatic rings contain from 8 to 12 carbon atoms, preferably 9 or 10 carbon atoms in the ring. Aromatic rings may be unsubstituted or substituted with from 1 to 4 substituents on the ring. Preferred aromatic ring substituents include: halo, cyano, alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. More preferred substituents include halo and haloalkyl. Preferred aromatic rings include naphthyl and phenyl. The most preferred aromatic ring is phenyl.

"Biohydrolyzable ester" is an ester moiety that does not interfere with the therapeutic activity of the compound, or that is readily metabolized by a human or mammal.

"Carbocyclic aliphatic ring" is a saturated or unsaturated hydrocarbon ring. Carbocyclic aliphatic rings are not aromatic. Carbocyclic aliphatic rings are monocyclic, or are fused, spiro, or bridged bicyclic ring systems. Monocyclic carbocyclic aliphatic rings contain from about 4 to about 10 carbon atoms, preferably from 4 to 7 carbon atoms, and most preferably from 5 to 6 carbon atoms in the ring. Bicyclic carbocyclic aliphatic rings contain from 8 to 12 carbon atoms, preferably from 9 to 10 carbon atoms in the ring. Carbocyclic aliphatic rings may be unsubstituted or substituted with from 1 to 4 substituents on the ring. Preferred carbocyclic aliphatic ring substituents include: halo, cyano, alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. More preferred substituents include halo and haloalkyl. Preferred carbocyclic aliphatic rings include cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl. More preferred carbocyclic aliphatic rings include cyclohexyl, cycloheptyl, and cyclooctyl. The most preferred carbocyclic aliphatic ring is cycloheptyl.

"Halo" is fluoro, chloro, bromo or iodo. Preferred halo are fluoro, chloro and bromo; more preferred are chloro and fluoro, especially fluoro.

"Haloalkyl" is a straight, branched, or cyclic hydrocarbon substituted with one or more halo substituents. Preferred haloalkyl are C_1-C_{12}; more preferred are C_1-C_6; more preferred still are C_1-C_3. Preferred halo substituents are fluoro and chloro. The most preferred haloalkyl is trifluoromethyl.

"Heteroalkyl" is a saturated or unsaturated chain containing carbon and at least one heteroatom, wherein no two heteroatoms are adjacent. Heteroalkyl chains contain from 1 to 18 member atoms (carbon and heteroatoms) in the chain, preferably 1 to 12, more preferably 1 to 6, more preferably still 1 to 4. Heteroalkyl chains may be straight or branched. Preferred branched heteroalkyl have one or two branches, preferably one branch. Preferred heteroalkyl are saturated. Unsaturated heteroalkyl have one or more double bonds and/or one or more triple bonds. Preferred unsaturated heteroalkyl have one or two double bonds or one triple bond, more preferably one double bond. Heteroalkyl chains may be unsubstituted or substituted with from 1 to 4 substituents. Preferred heteroalkyl are unsubstituted. Preferred heteroalkyl substituents include halo, hydroxy, aryl (e.g., phenyl, tolyl, alkyloxyphenyl, alkyloxycarbonylphenyl, halophenyl), heterocyclyl, heteroaryl. For example, alkyl substituted with the following substituents are heteroalkyl: alkoxy (e.g., methoxy, ethoxy, propoxy, butoxy, pentoxy), aryloxy (e.g., phenoxy, chlorophenoxy, tolyloxy, methoxyphenoxy, benzyloxy, alkyloxycarbonylphenoxy, acyloxyphenoxy), acyloxy (e.g., propionyloxy, benzoyloxy, acetoxy), carbamoyloxy, carboxy, mercapto, alkylthio, acylthio, arylthio (e.g., phenylthio, chlorophenylthio, alkylphenylthio, alkoxyphenylthio, benzylthio, alkyloxycarbonylphenylthio), amino (e.g., amino, mono- and di- C_1-C_3 alkanylamino, methylphenylamino, methylbenzylamino, C_1-C_3 alkanylamido, carbamamido, ureido, guanidino).

"Heteroatom" is a nitrogen, sulfur, or oxygen atom. Groups containing more than one heteroatom may contain different heteroatoms.

"Heterocyclic aliphatic ring" is a saturated or unsaturated ring containing carbon and from 1 to about 4 heteroatoms in the ring, wherein no two heteroatoms are adjacent in the ring and no carbon in the ring that has a heteroatom attached to it also has a hydroxyl, amino, or thiol group attached to it. Heterocyclic aliphatic rings are not aromatic. Heterocyclic aliphatic rings are monocyclic, or are fused or bridged bicyclic ring systems. Monocyclic heterocyclic aliphatic rings contain from about 4 to about 10 member atoms (carbon and heteroatoms), preferably from 4 to 7, and most preferably from 5 to 6 member atoms in the ring. Bicyclic heterocyclic aliphatic rings contain from 8 to 12 member atoms, preferably 9 or 10 member atoms in the ring. Heterocyclic aliphatic rings may be unsubstituted or substituted with from 1 to 4 substituents on the

ring. Preferred heterocyclic aliphatic ring substituents include: halo, cyano, alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. More preferred substituents include halo and haloalkyl. Preferred heterocyclic aliphatic rings include piperzyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and piperdyl.

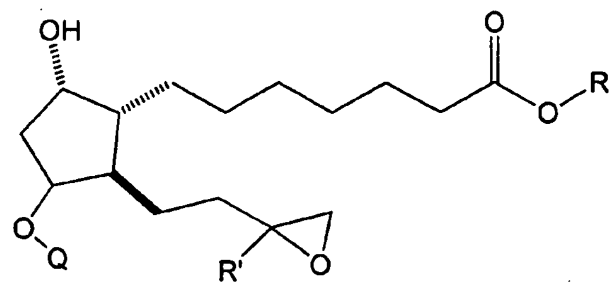
"Heteroaromatic ring" is an aromatic ring system containing carbon and from 1 to about 4 heteroatoms in the ring. Heteroaromatic rings are monocyclic or fused bicyclic ring systems. Monocyclic heteroaromatic rings contain from about 5 to about 10 member atoms (carbon and heteroatoms), preferably from 5 to 7, and most preferably from 5 to 6 in the ring. Bicyclic heteroaromatic rings contain from 8 to 12 member atoms, preferably 9 or 10 member atoms in the ring. Heteroaromatic rings may be unsubstituted or substituted with from 1 to 4 substituents on the ring. Preferred heteroaromatic ring substituents include: halo, cyano, alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. More preferred substituents include halo, haloalkyl, and phenyl. Preferred heteroaromatic rings include thienyl, thiazolo, purinyl, pyrimidyl, pyridyl, and furanyl. More preferred heteroaromatic rings include thienyl, furanyl, and pyridyl. The most preferred heteroaromatic ring is thienyl.

"Lower alkyl" is an alkyl chain radical comprised of 1 to 6, preferably 1 to 4 carbon atoms.

"Phenyl" is a six-membered monocyclic aromatic ring which may or may not be substituted with from about 1 to about 4 substituents. The substituents may be substituted at the *ortho*, *meta* or *para* position on the phenyl ring, or any combination thereof. Preferred phenyl substituents include: halo, cyano, alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. More preferred substituents on the phenyl ring include halo and haloalkyl. The most preferred substituent is halo. The preferred substitution pattern on the phenyl ring is *ortho* or *meta*. The most preferred substitution pattern on the phenyl ring is *ortho*.

The Novel Epoxide Intermediate

The present invention is directed to a process for making a novel Methyl 7-(2-hydroxy-5-(2-(2-oxiranyl)ethyl)-4-(1,1,2,2 tetramethyl-1-silapropoxy) cyclopentyl) heptanoate intermediate (the "epoxide intermediate") having the following general formula:



Formula I

wherein:

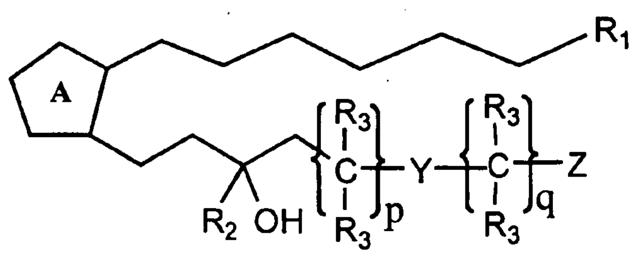
a) R is lower alkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring;

b) R' is hydrogen, lower alkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring provided the carbon at C_{15} (prostaglandin numbering) has only one heteroatom attached to it; and

c) Q is a suitable protecting group. Suitable protecting groups include tert-butyl dimethylsilyl, trimethylsilyl, benzyl, C_1-C_8 alkyl, or aromatic ether, or a benzoyl or acetyl ester. Preferred protecting groups include tert-butyl dimethylsilyl, trimethylsilyl, and benzyl ethers. The most preferred protecting group is a tert-butyl dimethylsilyl ether.

Compounds Prepared Using the Present Process

This epoxide intermediate above is useful for making 13,14-dihydro prostaglandin A, E and F derivatives. Thus, the invention is further directed to a process for making 13,14-dihydro prostaglandin A, E and F derivatives having the following general formula:



Formula II

wherein:

a) R_1 is CO_2H, C(O)NHOH, CO_2R_5, CH_2OH, $S(O)_2R_5$, $C(O)NHR_5$, $C(O)NHS(O)_2R_5$, or tetrazole; wherein R_5 is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring;

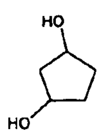
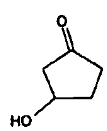
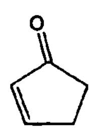
b) R_2 is hydrogen, lower alkyl carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring;

c) each R_3 is independently selected from the group consisting of: hydrogen, lower alkyl, alkoxy, haloalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, and heteroaromatic ring;

d) Y is NR_4, S, S(O), $S(O)_2$, O, or a bond wherein R_4 is hydrogen or lower alkyl;

e) p is 0-5, q is 0-5, and p+q is 0-5 provided that when Y is a bond p is at least 1;

f) Z is hydrogen, methyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring provided that when Y is NR_4, S, S(O), or $S(O)_2$ and q is 0, Z is not hydrogen;

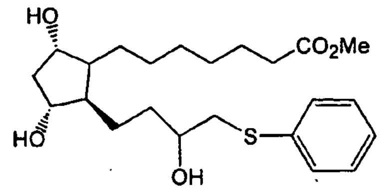
g) A is , , or ; and

h) provided the carbon at C_{15} (prostaglandin numbering) has only one heteroatom attached to it.

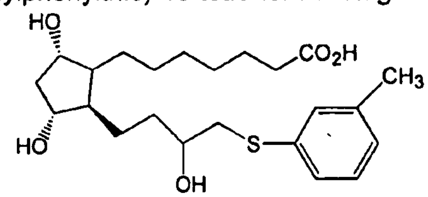
The 13,14-dihydro prostaglandin A, E and F derivatives described directly above may themselves be used as intermediates in the preparation of other 13,14-dihydro prostaglandin A, E or F derivatives. That is, the compounds prepared may be reacted further, using known chemistry, to yield other active derivatives, such as other PGA, PGE and PGF derivatives.

Compounds which may be prepared using the process of the present invention include, but are not limited to, those shown below:

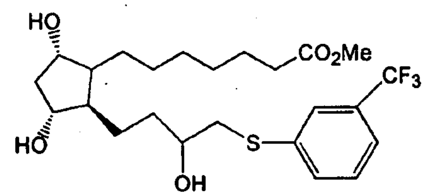
13,14-dihydro-16-(phenylthio)-16-tetranor Prostaglandin $F_{1\alpha}$ methyl ester:



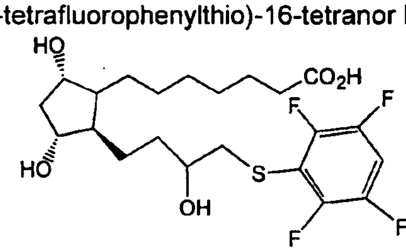
13,14-dihydro-16-(3-methylphenylthio)-16-tetranor Prostaglandin $F_{1}\alpha$:



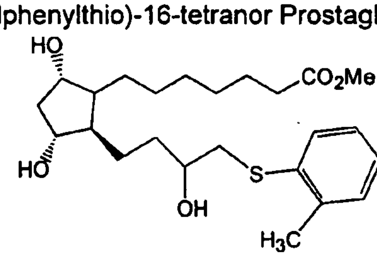
13,14-dihydro-16-(3-trifluoromethylphenylthio)-16-tetranor Prostaglandin $F_{1}\alpha$ methyl ester:



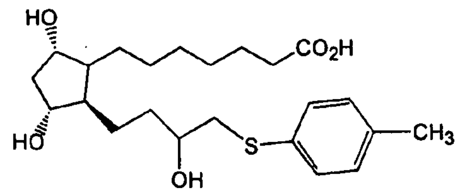
13,14-dihydro-16-(2,3,5,6-tetrafluorophenylthio)-16-tetranor Prostaglandin $F_{1}\alpha$:



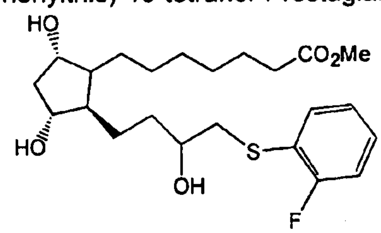
13,14-dihydro-16-(2-methylphenylthio)-16-tetranor Prostaglandin $F_{1}\alpha$ methyl ester:



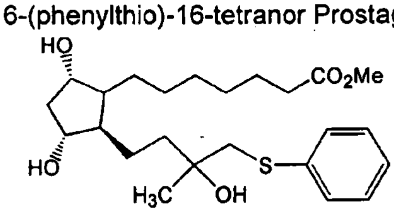
13,14-dihydro-16-(4-methylphenylthio)-16-tetranor Prostaglandin $F_{1}\alpha$:



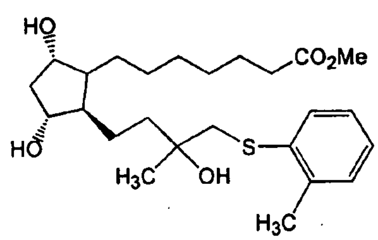
13,14-dihydro-16-(2-fluorophenylthio)-16-tetranor Prostaglandin $F_{1}\alpha$ methyl ester:



13,14-dihydro-15-methyl-16-(phenylthio)-16-tetranor Prostaglandin $F_{1}\alpha$ methyl ester:



13,14-dihydro-15-methyl-16-(2-methylphenylthio)-16-tetranor Prostaglandin $F_{1}\alpha$ methyl ester:



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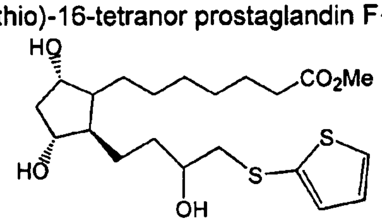
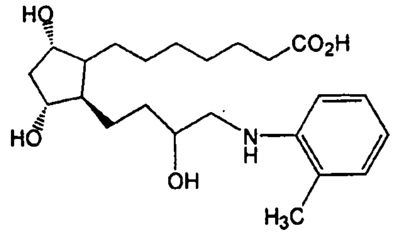
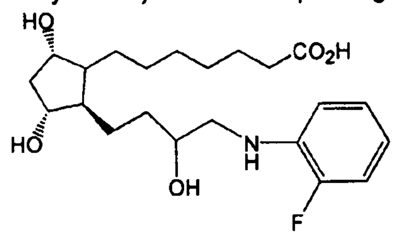


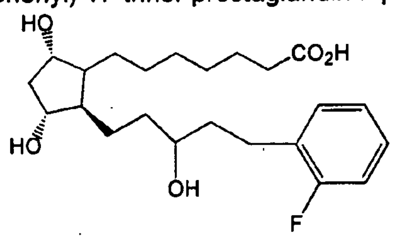
13,14-dihydro-16-(2-methylphenylamino)-16-tetranor prostaglandin $F_{1}\alpha$:



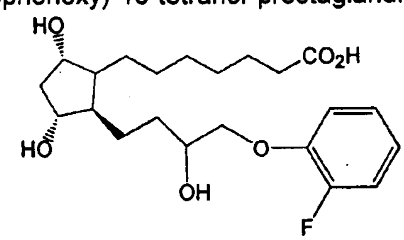
13,14-dihydro-16-(2-fluorophenylamino)-16-tetranor prostaglandin $F_{1}\alpha$:



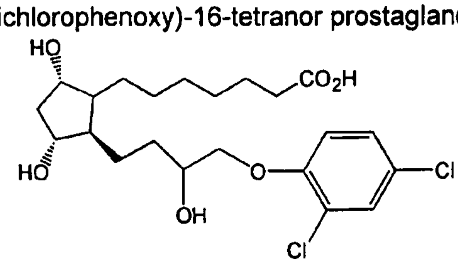
13,14-dihydro-17-(2-fluorophenyl) 17-trinor prostaglandin $F_{1}\alpha$:



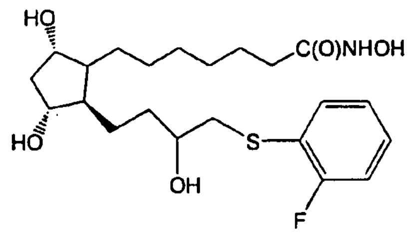
13,14-dihydro-16-(2-fluorophenoxy)-16-tetranor prostaglandin $F_{1}\alpha$:



13,14-dihydro-16-(2,4-dichlorophenoxy)-16-tetranor prostaglandin $F_{1}\alpha$:



13,14-dihydro-16-(2-fluorophenylthio)-16-tetranor Prostaglandin $F_{1}\alpha$ 1-hydroxamic acid:



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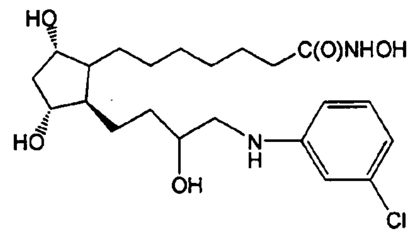
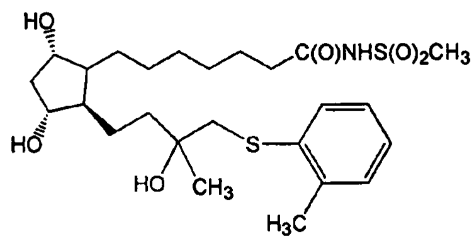
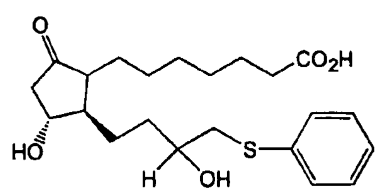


13,14-dihydro-15-methyl-16-(2-methylphenylthio)-16-tetranor Prostaglandin $F_{1\alpha}$ 1-N-methanesulfonamide:



13,14-dihydro-16-(phenylthio)-16-tetranor prostaglandin E_1:



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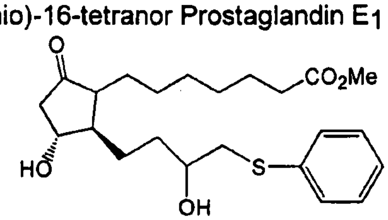
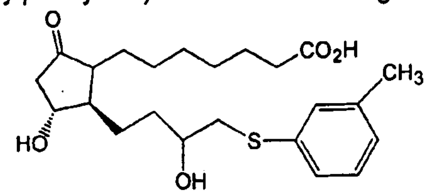


13,14-dihydro-16-(3-methylphenylthio)-16-tetranor Prostaglandin E_1:



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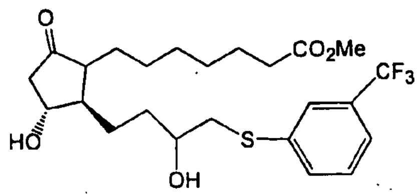
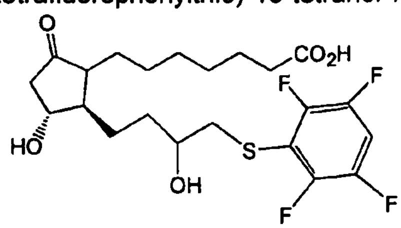
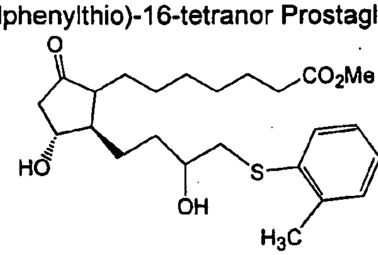


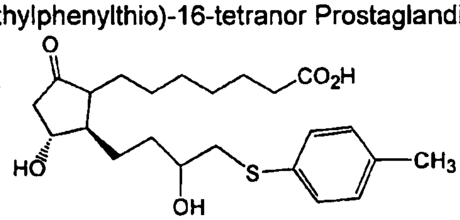
13,14-dihydro-16-(2,3,5,6-tetrafluorophenylthio)-16-tetranor Prostaglandin E_1:



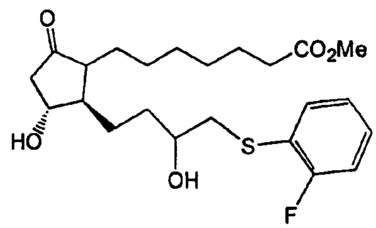
13,14-dihydro-16-(2-methylphenylthio)-16-tetranor Prostaglandin E_1 methyl ester:



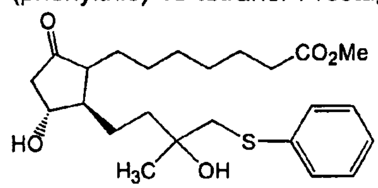
13,14-dihydro-16-(4-methylphenylthio)-16-tetranor Prostaglandin E_1:



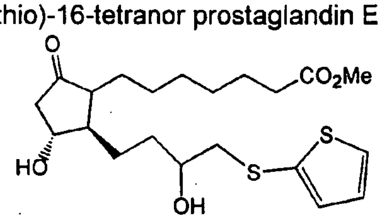
13,14-dihydro-16-(2-fluorophenylthio)-16-tetranor Prostaglandin E_1 methyl ester:



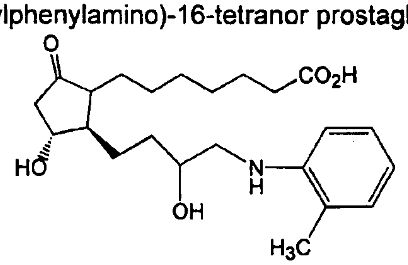
13,14-dihydro-15-methyl-16-(phenylthio)-16-tetranor Prostaglandin E_1 methyl ester:



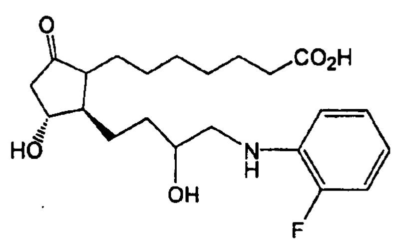
13,14-dihydro-16-(2-thienylthio)-16-tetranor prostaglandin E_1 methyl ester:



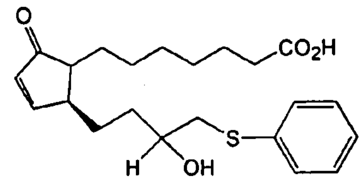
13,14-dihydro-16-(2-methylphenylamino)-16-tetranor prostaglandin E_1:



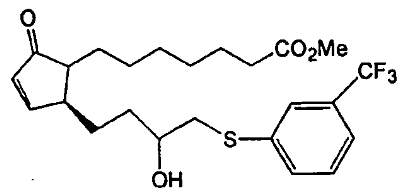
13,14-dihydro-16-(2-fluorophenylamino)-16-tetranor prostaglandin E_1:



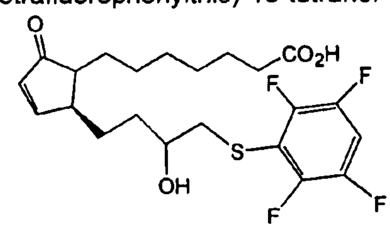
13,14-dihydro-16-(phenylthio)-16-tetranor prostaglandin A_1:



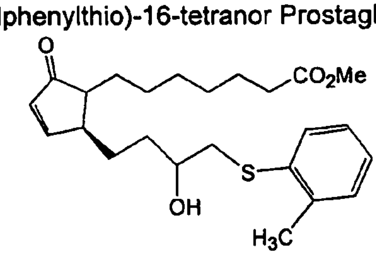
13,14-dihydro-16-(3-trifluoromethylphenylthio)-16-tetranor Prostaglandin A_1 methyl ester:



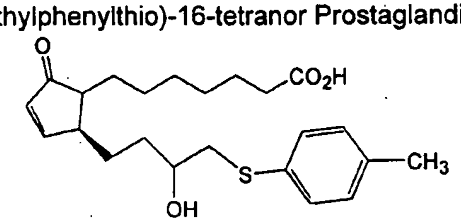
13,14-dihydro-16-(2,3,5,6-tetrafluorophenylthio)-16-tetranor Prostaglandin A_1:



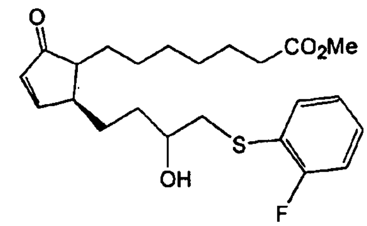
13,14-dihydro-16-(2-methylphenylthio)-16-tetranor Prostaglandin A_1 methyl ester:



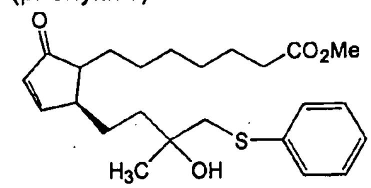
13,14-dihydro-16-(4-methylphenylthio)-16-tetranor Prostaglandin A_1:



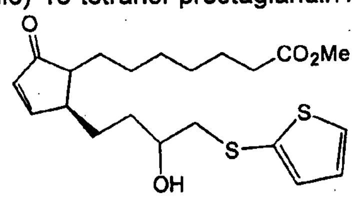
13,14-dihydro-16-(2-fluorophenylthio)-16-tetranor Prostaglandin A_1 methyl ester:



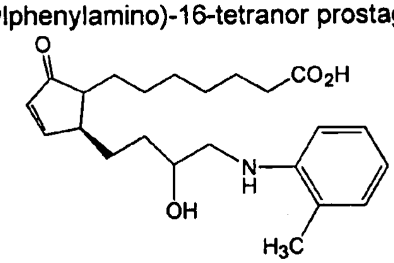
13,14-dihydro-15-methyl-16-(phenylthio)-16-tetranor Prostaglandin A_1 methyl ester:



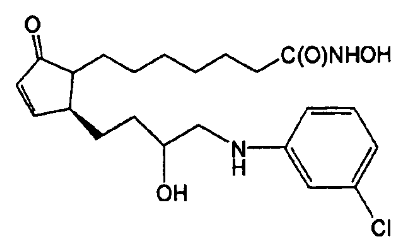
13,14-dihydro-16-(2-thienylthio)-16-tetranor prostaglandin A_1 methyl ester:



13,14-dihydro-16-(2-methylphenylamino)-16-tetranor prostaglandin A_1:



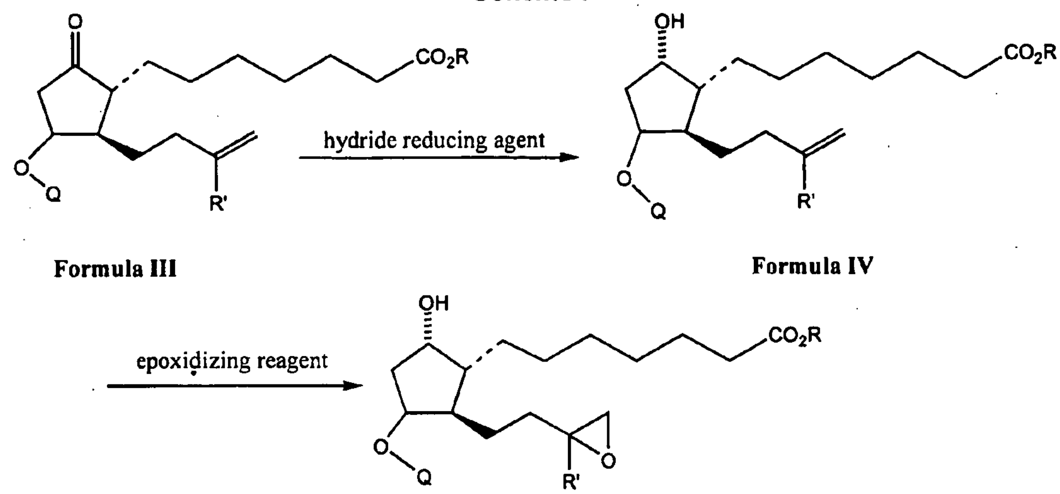
13,14-dihydro-16-(3-chlorophenylamino)-16-tetranor Prostaglandin A_1 1-hydroxamic acid:



Process for Making the Novel Epoxide Intermediate

The process for making the novel epoxide intermediates according to **Formula I** above is depicted below in the following general reaction scheme:

Scheme I



Formula III **Formula IV**

Formula I

The process depicted above in **Scheme I** begins with providing a compound according to **Formula III**. Compounds according to **Formula III** can be made from known starting materials and methods known to those skilled in the art. For example, the commercially available material Methyl 7-[3-(R)-hydroxy-5-oxo-1-cyclopent-1-yl] heptanoate (Cayman Chemical) can be modified according to processes exemplified by the following references: House, H.O.; Chu, C.Y.; Wilkins, J.M.; Umen, M.J. "The Chemistry of Carbanions. XXVII. A Convenient Precursor for the Generation of Lithium Organocuprates" J. Org. Chem. 1975, 40(10), p. 1460-1468.; 2) Knochel, P.; Jeong, N.; Rozema, M.J.; Yeh, M.C.P.: "Zinc and Copper Carbenoids as Efficient and Selective a^1/d^1 Multicoupling Reagents" J. Amer. Chem. Soc. 1989, 111, p. 6474-6476. A particularly preferred method for preparing such compounds is described below in **Example I**.

The next step in the process is modifying the compound according to **Formula III** to yield a compound according to **Formula IV**. The compound according to **Formula III** is treated with a hydride reducing agent, such as those reported in the art for PGF derivatives (see for example Davis et al., "A Convergent Total Synthesis of ($^+$-)-Prostaglandin $F_{2\alpha}$ via Conjugate Addition and Regiospecific Enolate Trapping" *J. Org. Chem.* 1979, 44(22), p.3755-3759). The ketone is reacted with a hydride reducing agent in a polar protic solvent to give the C_9 alcohol. "Hydride reducing agent" refers to any agent capable of delivering a hydride ion in a reaction. Preferred hydride reducing agents include L-selectride and sodium borohydride. The most preferred hydride

reducing agent is sodium borohydride. Preferred polar protic solvents include methanol, ethanol, and butanol. The most preferred polar protic solvent is methanol. The preferred temperature range for the reduction is between -100°C and 23°C. More preferred still is between -60°C and 0°C. The most preferred temperature range is between -45°C and -20°C.

The product alcohol so obtained can be isolated using methods known to those skilled in the art. Such methods include extraction, solvent evaporation, distillation, and crystallization procedures. Most preferably, the product is purified by flash chromatography on silica gel (Merck, 230-400 mesh) using 20% EtOAc/hexanes as the eluent.

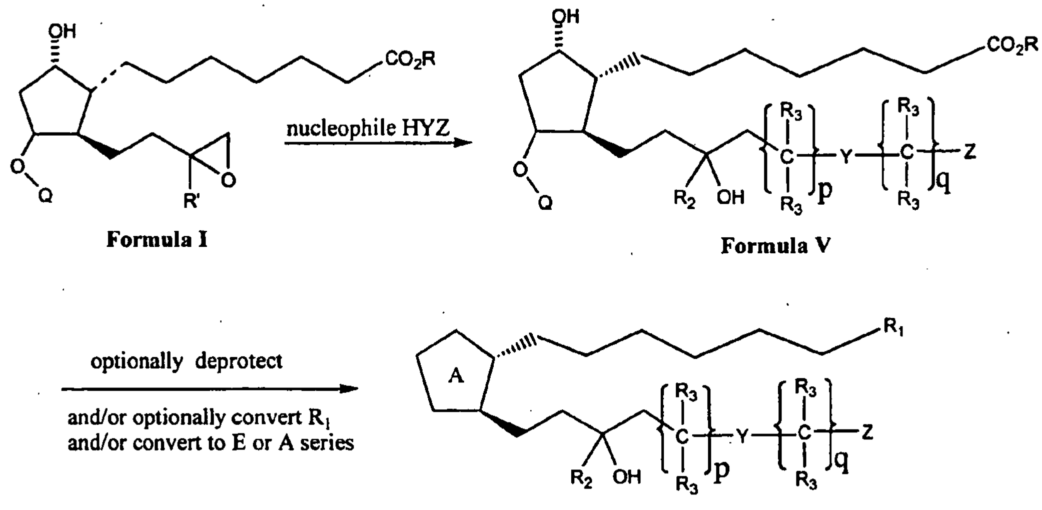
Finally, the compound according to **Formula IV** is then treated with an epoxidizing agent in a halocarbon solvent to provide a novel epoxide intermediate according to **Formula I**. "Epoxidizing agent" refers to a chemical capable of producing a 3-membered ring possessing one oxygen atom from a carbon-carbon double bond. Preferred epoxidizing agents include meta-chloroperbenzoic acid and peracetic acid. More preferred epoxidizing agents include meta-chloroperbenzoic acid and peracetic acid. The most preferred epoxidizing agent is meta-chloroperbenzoic acid. "Halocarbon solvent" refers to a solvent which has one or more halogens attached to a carbon chain. Preferred halocarbon solvents include dichloromethane, dichloroethane, carbon tetrachloride, and chloroform. More preferred halocarbon solvents include dichloromethane and chloroform. The most preferred halocarbon solvent is dichloromethane.

The epoxide intermediates according to **Formula I** can be isolated using methods known to those skilled in the art. Such methods include extraction, solvent evaporation, distillation, or crystallization procedures. Most preferably, the product is purified by flash chromatography on silica gel (Merck, 230-400 mesh) using 20% EtOAc/hexanes as the eluent.

Process for Making 13,14-dihydro prostaglandin A, E, and F Derivatives

The process for making the 13,14-dihydro prostaglandin A, E, and F derivatives according to **Formula II** above is depicted below in the following general reaction scheme:

Scheme II



Formula I
Formula V
Formula II

The novel epoxide intermediates according to **Formula I** can be reacted with a variety of carbon, oxygen, sulfur and nitrogen containing nucleophiles ("nucleophile HYZ") as described in the art to provide C_{11}-protected 13,14-dihydro-15-substituted-16-substituted tetranor prostaglandin A, E, and F derivatives (see for example: Smith, J.G., "Synthetically Useful Reactions of Epoxides", Synthesis 1984, p.629-656). "Nucleophile HYZ" refers to any chemical agent suitable for adding to an epoxide to form a covalent bond in a ring-opening process. Preferred nucleophiles include 2-thienyl mercaptan, *o,m,p*-chlorophenol, ethyl mercaptan, *o,m,p*-lithio chlorobenzene, morpholine, thiophenol, aniline, *o,m,p*-toluidine, o,m,p-chloro thiophenol, *o,m,p*-fluoro thiophenol, *o,o*-dichloro thiophenol, phenylurethane, *o,m,p*-trifluoromethyl thiophenol, furfuryl amine, benzyl amine, furfuryl alcohol, and 2-amino pyridine. More preferred nucleophiles include thiophenol, *o*-chloro thiophenol, and aniline. The most preferred nucleophile is *o*-F-thiophenol.

Deprotection at C_{11} can then be carried out when the compound according to **Formula I** is intended to be a PGF derivative. "Deprotection" refers to the removal of protecting groups used to protect sensitive functional groups. Deprotection includes the removal of silyl ethers of alcohols or alkyl esters of carboxylic acids.

Conversion of the R ester of the **Formula V** compound to the desired R_1 of **Formula II** can be carried out using methods known to those skilled in the art. Such methods include, but are not limited to, deprotection of C_{11}, deprotection of C_1, selective oxidation of C_9, reduction of C_1, base catalyzed elimination of the C_{11} alcohol, condensation of C_1 with amines, and condensation of C_1 with hydroxylamines.

Conversion to a PGE derivative from the corresponding PGF derivative according to **Formula II** can be carried out by oxidization at C_9 using methods known to

those skilled in the art. Conversion to a PGA derivative from the corresponding PGE derivative can be carried out by elimination of the C_{11} alcohol using methods known to those skilled in the art.

Addition of sulfur and oxygen nucleophiles is carried out in the presence of base. "Base" means a basic reagent which is added to the reaction mixture to facilitate covalent bond formation and ring-opening of the epoxide and the nucleophile. Bases include nitrogen bases. Preferred bases include those which are soluble in organic solvents and are volatile. Specifically, preferred bases include N,N diisopropylethylamine, triethylamine, trimethylamine, butylamine, pyridine, and 2,6-lutidine. The more preferred bases are 2,6-lutidine, triethylamine, and pyridine. The most preferred base is triethylamine. The reaction is carried out preferably at between 150°C and 0°C, more preferably between 120°c and 20°C and most preferably between 80°C and 50°C. The preferred organic solvents for the reaction are aromatic hydrocarbon solvents. More preferred organic solvents include xylenes, toluene, and benzene. The most preferred organic solvent is benzene.

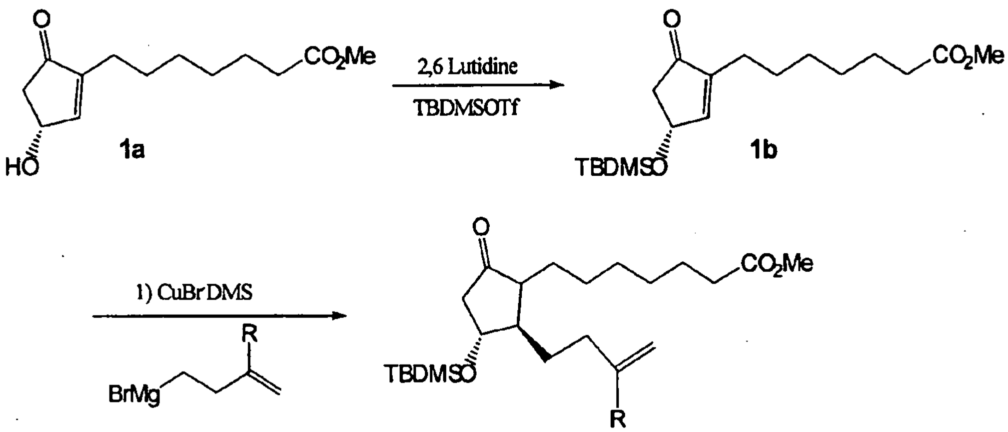
Addition of nitrogen nucleophiles is carried out in the presence of a Lewis acid and a polar aprotic solvent or with no solvent. "Lewis acid" refers to any non-protic acid which is added to the reaction mixture to facilitate covalent bond formation and ring-opening of the epoxide with the nucleophile. The preferred Lewis acids include magnesium perchlorate, boron trifluoride etherate, titanium tetrachloride and triethylaluminum. The most preferred Lewis acid is magnesium perchlorate. Polar aprotic acids include N,N dimethylformamide and ethereal solvents. "Ethereal solvent" refers to a solvent which has two alkyl groups bonded to an oxygen including those in which the alkyl group and oxygen are part of a ring. Preferred ethereal solvents include diethyl ether and tetrahydrofuran. The most preferred ethereal solvent is tetrahydrofuran. The most preferred polar aprotic solvent is N,N dimethylformamide. The preferred reaction temperature is between 150°C and 23°C. The more preferred reaction temperature is between 125°C and 40°C. The most preferred temperature is between 100°C and 75°C.

Addition of carbon nucleophiles generated from the anion is carried out in the presence of a Lewis acid and an ethereal solvent. Preferred ethereal solvents include diethyl ether and tetrahydrofuran. The most preferred ethereal solvent is tetrahydrofuran. The most preferred Lewis acid with carbon nucleophiles is boron trifluoride-etherate.

The following non-limiting examples illustrate the processes of the present invention:

Example 1

Preparation of Formula III Compounds:



Formula III

Methyl 7-(2-oxo-4-(1,1,2,2-tetramethyl-1-silapropoxy)cyclopent-1-enyl) heptanoate 1b:

To a solution of Methyl-7-[3-(R)-hydroxy-5-oxo-1-cyclopenten-1-yl] heptanoate **1a** (1 equiv.) in CH_2Cl_2 at -78°C is added 2,6 Lutidine (1.3 equiv.) dropwise over 15 minutes. The solution is kept at -78°C and TBDMS Triflate (1.2 equiv.) in CH_2Cl_2 is added dropwise over 15 minutes. The reaction is warmed gradually to room temperature and stirred at room temperature for 15 hours. Aqueous 10% HCl is added and the layers are separated. The water layer is extracted with CH_2Cl_2 and the organic layers are combined. The organic layer is washed with brine, dried (Na_2SO_4) and concentrated. The residue is distilled under vacuum (house vacuum, 10 mm Hg) to provide 89% of the silyl ether **1b**.

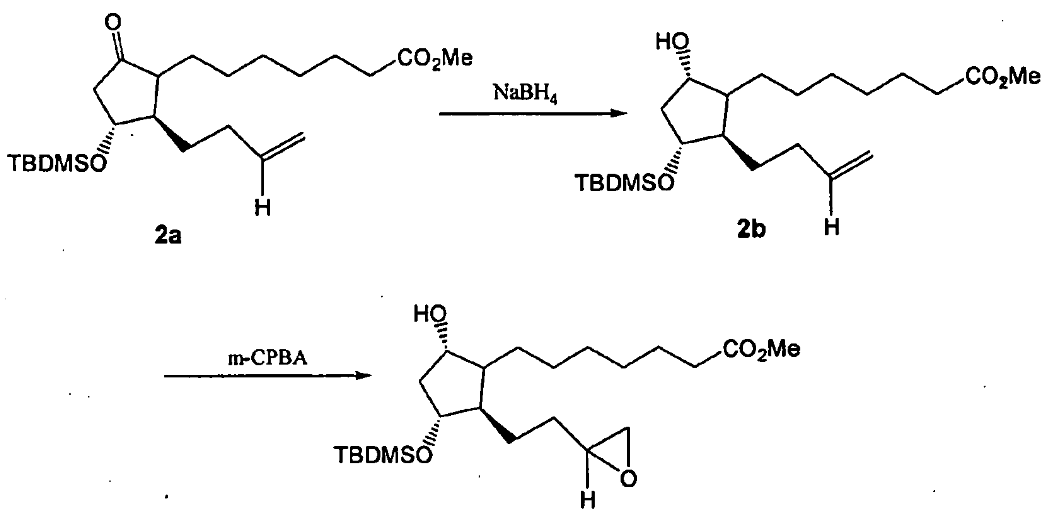
Compounds according to Formula III

To a slurry of Mg^0 powder (2 equiv.) in THF at room temperature is added one crystal of I_2 and the appropriate bromide (2equiv.) dropwise over 10 minutes. Preferred bromides include 1-bromobutene, 1-bromo-3-methyl-butene, and 1-bromo-3-ethylbutene. The reaction exotherms as the addition continues. After the addition is complete, the reaction is refluxed for 3 hours and cooled to room temperature. The Grignard is diluted with THF and added via cannula to a 3-necked flask equipped with mechanical stirring and charged with CuBr.DMS (2 equiv.) in a 1:1 solution of THF/DMS

at -78°C. After the addition of the Grignard (~20 min), the reaction is stirred 1 hour at -78°C. The color of the reaction is dark red at this point. A solution of the ketone **1b** (1 equiv.) in THF is then added dropwise over 25 minutes. The reaction is stirred at -78° C for 15 minutes, then allowed to warm slowly to room temperature over 2 hours. The reaction is quenched with aq. NH_4Cl and the excess DMS allowed to evaporate overnight. The reaction is partitioned between brine/CH_2Cl_2 and the layers separated. The aqueous layer is back-extracted with CH_2Cl_2 and the organic layers are combined and dried (Na_2SO_4). The solvent is removed in vacuo and the residue chromatographed on SiO2 (10 % hexane/EtOAc) to give 71% of the appropriate ketone according to **Formula III**.

Example 2

Preparation of Methyl 7-(2-hydroxy-5-(2-(2-oxiranyl)ethyl-4-(1,1,2,2-tetramethyl-1 silapropoxy)cyclopentyl) heptanoate 2c



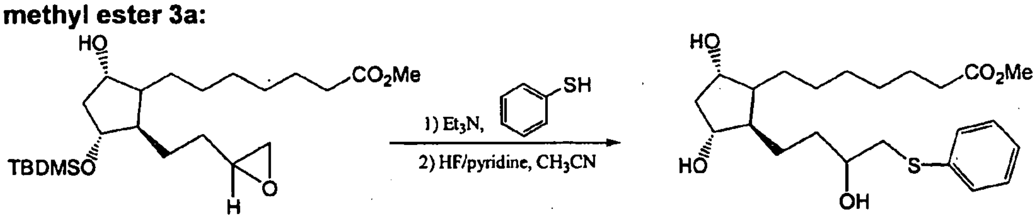
2a **2b** **2c**

The ketone **2a** (1 equiv.) is dissolved in MeOH and cooled to -40°C. Sodium borohydride (0.9 equiv.) is added portionwise over 10 minutes. After the addition is complete the reaction is stirred for 13 hours at -40°C and then 12 hours at -78°C. The reaction is quenched with water, partitioned between brine and CH_2Cl_2 and the layers separated. The aqueous layer is back-extracted with CH_2Cl_2 and the organic layers combined and dried (Na_2SO_4). The solvent is removed in vacuo and the residue chromatographed on SiO_2 (30 % EtOAc/hexanes) to give 75% of the alcohol **2b**.

The alcohol **2b** (1 equiv.) is dissolved in CH_2Cl_2 and cooled to 0^oC. Sodium bicarbonate is added, followed by m-CPBA (57%-85% purity) (3 equiv.) portionwise over 15 minutes. After the addition is complete the reaction is stirred for 20 hours at room temperature. The reaction is poured onto water, partitioned between brine and CH_2Cl_2 and the layers separated. The aqueous layer is back-extracted with CH_2Cl_2 and the organic layers combined and dried (Na_2SO_4). The solvent is removed in vacuo and the residue chromatographed on SiO_2 (20% EtOAc/hexanes) to give 73% of the epoxide diasteriomers **2c.**

Example 3

Preparation of 13,14-dihydro-16-(phenylthio)-16-tetranor prostaglandin $F_{1\alpha}$ methyl ester 3a:

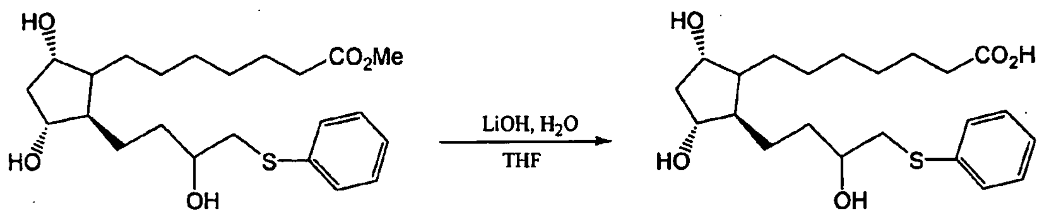


2c **3a**

In a 5 ml round bottomed flask epoxide **2c** (1 equiv.) and dry benzene are added. The flask is cooled to 0°C, then is treated with thiophenol (1.2 equiv.) and triethyl amine (1.2 equiv.). The ice bath is removed and the reaction stirred at room temperature under nitrogen over night. TLC is used to monitor the reaction. An excess amount of thiophenol is added if necessary. The reaction is quenched with brine, and extracted with methylene chloride, The organic layer is washed three times with 1N HCl, brine, dried (Na2SO4), and concentrated. Without further purification, to this crude reaction mixture, CH_3CN and HF/Pyridine are added while the flask is kept at 0°C. After 3 hours at 0°C, the reaction is quenched with saturated NaCl. The aqueous layer is extracted three times with CH_2Cl_2, the organic layers are combined and washed three time with 1N HCl, brine, dried (Na2SO4) and concentrated. After column (7:3, Hexane: Ethyl Acetate) 63% of **3a** is obtained.

Example 4

Preparation of 13,14-dihydro-16-(phenylthio)-16-tetranor prostaglandin $F_{1\alpha}$ 4a:

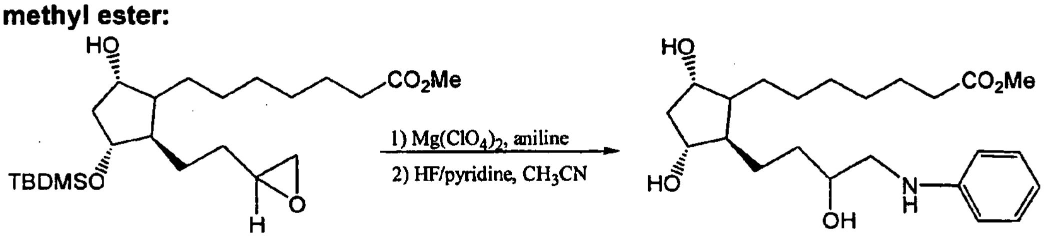


3a 4a

To a 5 ml round bottomed flask, 13,14-dihydro-16-(phenylthio)-16-tetranor Prostaglandin $F_{1}\alpha$ methyl ester and THF/water solution (3:1, THF : H_2O) are added, the flask is cooled at 0°C, then an excess (2.5 eg) amount of lithium hydroxide is added. The ice bath is removed, and the reaction stirred at room temperature over night. Methylene chloride and saturated citric acid are added to the reaction mixture, the aqueous layer is washed 3 times with methylene chloride, the organic layers are combined and are washed with brine, dried (Na_2SO_4), and chromatographed (methylene chloride, methanol, acetic acid, 9.6, 0.4, 0.015), **4a** is recovered in 63% yield.

Example 5

Preparation of 13,14-dihydro-16-(phenylamino)-16-tetranor prostaglandin $F_{1}\alpha$ methyl ester:

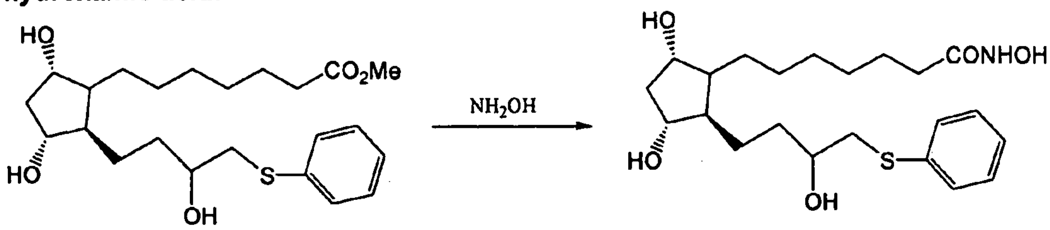


2c 5a

To a 10 ml round bottomed flask epoxide **2c** (1 equiv.), aniline (1.5 equiv.), catalytic magnesium perchlorate, and THF are added. After the reaction is refluxed under nitrogen overnight, the reaction is done. The flask is cooled to room temperature, and the solvent removed in vacuo. Without further purification to this crude reaction mixture, CH_3CN and HF/Pyridine (0.6 equiv.) are added while the flask is kept at 0°C. After 5 hours at 0°C, the reaction is quenched with saturated NaCl. The aqueous layer is extracted three times with CH_2Cl_2, the organic layers are combined and washed three time with saturated $NaHCO_3$, brine, and dried (Na_2SO_4). After column (95% CH_2Cl_2, 5% MeOH) **5a** is recovered in 50% yield.

Example 6

Preparation of 13,14-dihydro-16-(phenylthio)-16-tetranor Prostaglandin $F_{1\alpha}$ 1-hydroxamic acid:

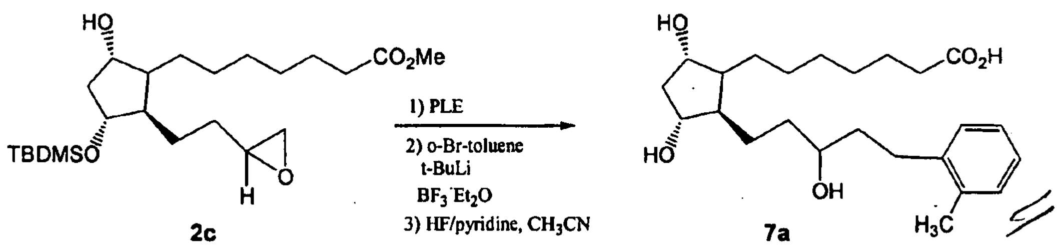


3a 6a

In a flame-dried 25 mL round-bottomed flask equipped with a magnetic stir bar is placed 13,14-dihydro-16-(phenylthio)-16-tetranor Prostaglandin $F_{1\alpha}$ methyl ester **3a** (1.0 equiv.) in methanol. To this solution is added hydroxylamine in methanol (1.25 equiv.). The solution stirred for 18 hours. The solution is then treated with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer is washed with brine, dried over anhydrous MgSO4, filtered and concentrated under reduced pressure. The residue is purified by chromatography to give 13,14-dihydro-16-(phenylthio)-16-tetranor Prostaglandin $F_{1\alpha}$ 1-hydroxamic acid **6a**.

Example 7

Preparation of 13,14-dihydro-17-(2-methylphenyl) 17-trinor prostaglandin $F_{1\alpha}$



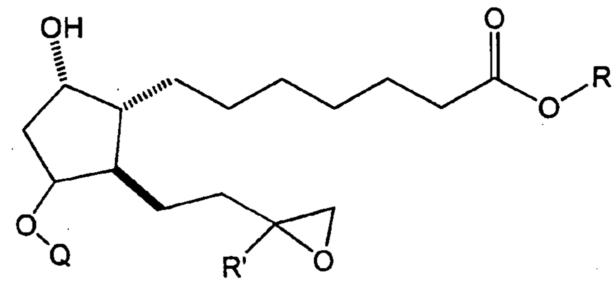
2c 7a

The epoxide **2c** is treated with pig liver esterase to remove the methyl ester. Then, to a 10 ml round bottomed flask at -78 °C, the acid and $BF_3 \cdot Et_2O$ are stirred, then the lithio anion of o-bromotoluene(1.5 equiv.), in THF are added. After the reaction is stirred at -30°C under nitrogen for several hours, the reaction is done. The reaction is quenched with saturated NH_4Cl, and the solvent removed in vacuo. Without further purification to this crude reaction mixture, CH3CN and HF/Pyridine (0.6 equiv.) are added while the flask is kept at 0°C. After 5 hours at 0°C, the reaction is quenched with saturated NaCl. The aqueous layer is extracted three times with CH_2Cl_2, the

organic layers are combined and washed three time with saturated $NaHCO_3$, brine, and dried (Na_2SO_4). After column (95% CH_2Cl_2, 5% MeOH) of product **7a** is recovered in 50% yield.

What is claimed is:

1. A method of preparing a compound having the structure:

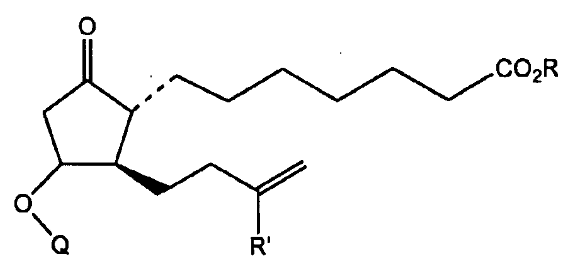


characterized in that
R is lower alkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring;

R' is hydrogen, lower alkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring provided the carbon at C_{15} (prostaglandin numbering) has only one heteroatom attached to it; and

Q is a suitable protecting group,

comprising the steps of:
a) providing a compound having the structure:



characterized in that
R is lower alkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring;

R' is hydrogen, lower alkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring provided the carbon at C_{15} (prostaglandin numbering) has only one heteroatom attached to it; and

Q is a suitable protecting group;

b) adding a hydride reducing agent to the compound provided in step a; and

c) adding an epoxidizing agent to the product of step b.

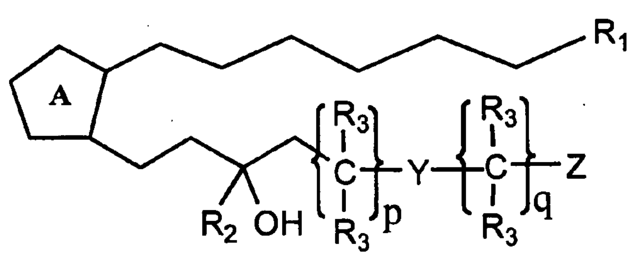
2. The method of Claim 1 characterized in that the hydride reducing agent is selected from the group consisting of L-selectride and sodium borohydride.

3. The method of Claim 2 characterized in that the epoxidizing agent is selected from the group consisting of meta-chloroperbenzoic acid and peracetic acid.

4. The method of Claim 3 characterized in that the hydride reducing agent is sodium borohydride and the epoxidizing agent is meta-chloroperbenzoic acid.

5. The method of Claim 1, 2, 3, or 4 characterized in that the step of adding a hydride reducing agent is carried out in a temperature range from -45°C to -20°C.

6. A method of preparing a prostaglandin derivative having the structure:



characterized in that
R_1 is CO_2H, C(O)NHOH, CO_2R_5, CH_2OH, $S(O)_2R_5$, $C(O)NHR_5$, $C(O)NHS(O)_2R_5$, or tetrazole; characterized in that R_5 is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring;

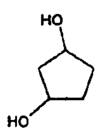
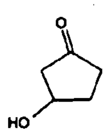
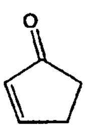
R_2 is hydrogen, lower alkyl carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring;

each R_3 is independently selected from the group consisting of: hydrogen, lower alkyl, alkoxy, haloalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, and heteroaromatic ring..

Y is NR_4, S, S(O), $S(O)_2$, O, or a bond characterized in that R_4 is hydrogen or lower alkyl;

p is 0-5, q is 0-5, and p+q is 0-5 provided that when Y is a bond p is at least 1;

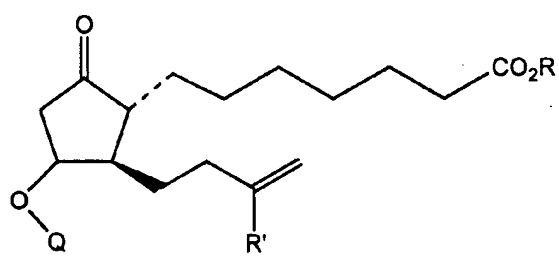
Z is hydrogen, methyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring provided that when Y is NR_4, S, S(O), or $S(O)_2$ and q is 0, Z is not hydrogen;

A is , , or ; and

provided the carbon at C_{15} (prostaglandin numbering) has only one heteroatom attached to it,

comprising the steps of:

a) providing a compound having the structure:



characterized in that

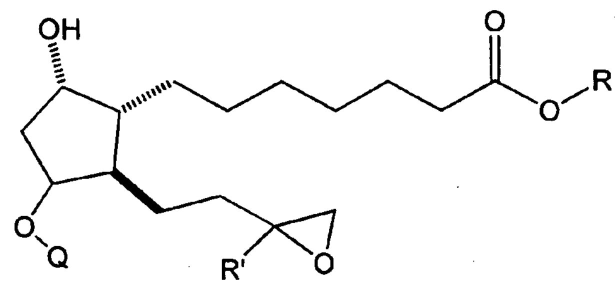
R is lower alkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring;

R' is hydrogen, lower alkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring provided the carbon at C_{15} (prostaglandin numbering) has only one heteroatom attached to it; and

Q is a suitable protecting group;

b) adding a hydride reducing agent to the compound provided in step a; and

c) adding an epoxidizing agent to the product of step b to yield a compound having the structure:



characterized in that

R is lower alkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring;

R' is hydrogen, lower alkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring provided the carbon at C_{15} (prostaglandin numbering) has only one heteroatom attached to it; and

Q is a suitable protecting group,

d) opening the epoxide ring with an appropriate nucleophile; and

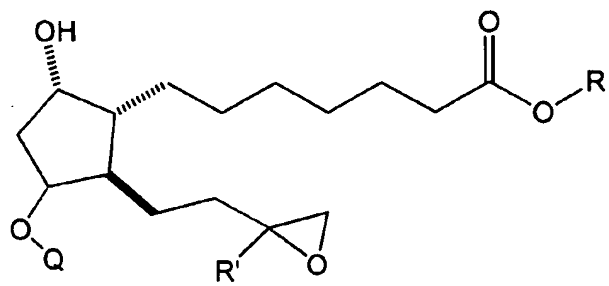
e) conducting one or more subsequent synthetic steps on the product of step d to form the desired prostaglandin derivative.

7. The method of Claim 6 characterized in that the nucleophile is a substituted or unsubstituted thiophenol or a substituted or unsubstituted aniline.

8. The method of Claim 7 characterized in that the one or more subsequent synthetic steps is selected from the group consisting of: deprotection of C_{11}, deprotection of C_1, selective oxidation of C_9, reduction of C_1, base catalyzed elimination

of the C_{11} alcohol, condensation of C_1 with amines, and condensation of C_1 with hydroxylamines.

9. A compound having the structure:



characterized in that

a) R is lower alkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring;

b) R' is hydrogen, lower alkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring provided the carbon at C_{15} (prostaglandin numbering) has only one heteroatom attached to it; and

c) Q is a suitable protecting group.

10. The compound of Claim 10 characterized in that R is methyl and Q is tert-butyl dimethyl silyl.

INTERNATIONAL SEARCH REPORT

In tional Application No
PCT/US 98/18593

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C405/00 //A61K31/557

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	A.L. WATERHOUSE ET AL.: "STRUCTURAL ASPECTS OF RYANODINE ACTION AND SELECTIVITY." JOURNAL OF MEDICINAL CHEMISTRY, vol. 30, 1987, pages 710-716, XP002085203 WASHINGTON US See scheme II --- -/--	1-10

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 November 1998	09/12/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Berte, M

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INTERNATIONAL SEARCH REPORT

In tional Application No
PCT/US 98/18593

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	D. DESMAELE ET AL.: "INFLUENCE DE LA SUBSTITUTION EN 1 SUR LA STEREOSELECTIVITE DE L' HYDROLYSE DE N,N DIETHYLAMINO-7 DIALKYL-1,6 BICYCLO (3,2,0) HEPTENE-6-ONES-2; UNE NOUVELLE VOIE D'ACCESS AU CONTROLE DES CENTRES C17 ET C20 DE STEROIDES." TETRAHEDRON LETTERS, vol. 24, no. 30, 1983, pages 3079-3083, XP002085204 OXFORD GB See p. 3081, comp. 12 --> 13	1-10

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